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A moving mesh study for diffusion induced effects in avascular tumour growth

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ABSTRACT

Studying the dynamical evolution of complex systems as biological ones from the continuum point of view, requires monitoring several parameters involved, whose modelling leads to system of non linear coupled partial differential equations. The interaction of the urokinase plasminogen activator system with a model for cancer cell in the avascular phase is faced with the moving mesh partial differential equation numerical technique, monitoring the dynamical evolution of the system as a function of the diffusion properties of cancer cells and of cell proliferation factor, over a one-dimensional biological domain. The computations are consistent with previous results, confirming that cancer proliferation in the very early stage of invasion occurs through highly irregular spatio-temporal pattern, which depends essentially on cancer motility characteristics, but non-obvious effects are observed which depend on the model proliferation parameters.

1. Introduction

The study of the cancer disease is emblematic of multidisciplinary approach in scientific research; modelling solid tumours dynamics, in fact, from the initial avascular phase up to the formation of new vasculature necessary to the tumour progression, requires contributions coming not only from biologists, physicians, pharmacologists, but approaches from the mathematics, physics, chemistry, etc. points of view became essential nowadays. In recent years, *in silico* modelling of tumour growth and progression has known a fast increase, and the mathematical modelling of biological systems constituted by cancer cells surrounded by healthy tissue can be improved, with numerical simulations providing ever more reliable results, if ever more efficient and effective numerical techniques are developed. The initial growth of solid tumours is characterized by the avascular phase, in which cancer cells start clustering multicellular spheroids [1–4], feeding from the surrounding healthy tissue. The tumour progression switches to the vascular phase [5,6] when cancer cells stimulate the angiogenesis, i.e. the creation of new blood vessels, giving the tumour the capability to attract more nutrients [7–11]. At this stage the malignant imprinting of tumour becomes evident, as the speed of invasion of the healthy tissue increases, and the network of new blood vessels allows cancer cells to disseminate away from the initial cancer seeding, beginning metastasis [12,13]. We address the interested reader to Refs. [14–18] for recent reviews about mathematical modelling of cancer cell growth and proliferation.

Here we will focus on a continuum model of avascular tumour growth: at tissue level, in fact, the Continuum Mechanics approach is appropriate, and the modelling leads to systems of non-linear, coupled partial differential equations (PDE) to be solved numerically, even if discrete and hybrid continuum/discrete approaches are also possible [19]. In this respect, the Finite Element Method (FEM) [20] is a powerful tool for the numerical integration of systems of PDE, suitable for numerical

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resolution in one-, two- and three-dimensional domains: they are discretized in elements delimited by nodes on which the problem is solved, but inside each element, the spatial variation of the solution is interpolated by means of interpolation, or shape, functions. The use of appropriate meshing techniques, enhances the quality of the domain discretization, resulting in overall resolution improvement and efficiency. Uniform discretization of the integration domain can be useful when the problem solution exhibits smooth spatial variations, but in presence of steep gradient of the solution process, adaptive meshing allows to obtain more reliable numerical results. Adaptive discretizations can be p-type, h-type or r-type [21]: the first two belong to the class of static remeshing techniques, while the latter are known as dynamic remeshing techniques. Static remeshing techniques are appropriate when the spatial variation of the solution is known, or can be reasonably guessed: the interpolation order (p-type), or the node density (h-type), is increased in regions of increasing solution gradient; quite often, such regions are *a priori* unknown, then r-type adaptive remeshing techniques become diriment, as the node distribution inside the integration domain is driven by the solution process itself, without external interventions, clustering the node points automatically according to a suitable parameter. Static remeshing techniques can be limited by smoothness requirements during the solution process, or by undesired huge amount of grid points; using dynamic remeshing techniques, instead, the latter are kept constant but moved towards regions where more detail is needed, increasing the overall resolution with computational saving. The Moving Mesh PDE (MMPDE) numerical technique, belonging to the class of dynamic remeshing techniques, relies on the monitor function, a quality functional controlling the mesh point distribution, which is computed during the solution process. Its suitability for studying highly frustrated physical systems [22–26], and complex biological ones as in the case of cancer cell proliferation and growth [27–29], has been recently demonstrated.

The general modelling of cancer growth and proliferation requires a multi-scale approach from the microscopic level, where sub cellular mechanisms (DNA degradation, gene expression, nutrient absorption) activates, through phenomena occurring at the mesoscopic scale such as intercellular interactions in both tumour and healthy cells, up to the tissue level [30–32].

The extracellular matrix (ECM) is an aqueous environment providing cells with nutrients like proteins, oxygen, glucose, and where, upon chemical signalling, cancer cells start to proliferate [30]. Cells movement in biological system can be of random type, according to a diffusion coefficient; or it can be driven by concentration gradient of sensed chemicals as with chemotaxis, occurring when cells move towards the source of such species dissolved in ECM. Haptotaxis, in addition, occurs when the cells bind to chemicals which are not in solution, but in turn adhered to some ECM component: the cell/chemical/component complex then moves towards ECM regions where other components, with the same chemical bounded but with higher concentrations, are present, and on which the transported cell can jump and eventually bind.

The model we discuss takes into account chemotactic and haptotactic contributions to cancer cell movement inside ECM, in which the urokinase plasminogen activator (uPA) system is coupled to a model for cancer cells invasion [33,34]. The macromolecule vitronectin (VN) is a protein component of ECM in which degradation, when cancer cells start to invade the healthy tissue, is caused by the uPA serine protease, an enzyme catalyzing the proteolysis of ECM macromolecules [35,36]; formerly, cancer cells secrete the pro-uPA inactive enzyme, while the plasminogen ubiquitous protein, once activated to plasmin, become an ECM degrading enzyme which in turn activate pro-uPA to uPA; both uPA and pro-uPA bind to the cancer cell surface through the receptor uPAR. The healthy cells regulate the excess of proteolysis induced by uPA, by secreting a specific inhibitor, the plasminogen activator inhibitor type-1 (PAI-1) [33].

Knowing the tumour spatial extension is of key importance for both surgical and therapeutic treatments, considering, for instance, the importance of an exact localization for a successful targeted radiotherapy in the early stages of the tumour formation. The mathematical modelling contributes to predict the tumour dynamics with the help of sophisticated numerical techniques as in the case of the MMPDE, where the monitor function, peculiar of the technique, allows a tuning of the node distribution inside the integration domain according to the gradient of the cancer cell density, computed during the iterative solution process; it results an overall mesh quality increase by means of automatic refinement in spatial regions where the cancer cell density increases, i.e. moving the grid points where more details are required [22].

We consider the interaction of the uPA system with a cluster of cancer cells immersed in the ECM in the early stage of the tumour formation [27], hence in the avascular phase: in the frame of the mixture theory formulation for the mass conservation, it is represented by a system of five coupled, non-linear PDEs, which we solve using the MMPDE numerical technique over a one-dimensional integration domain discretized according to the gradient of the cancer cell density. The numerical results, although obtained for a simplified one-dimensional domain, reveal details of the tumour dynamics as a function of the motility characteristics of cancer cells. As expected, malignancy appears to be related with the increasing speed of invasion of the healthy tissue, and also with strong irregularities at the interface between healthy and cancer cells, but, with respect to previous simulations [27], we improve the model by considering possible pathophysiological effects on cancer proliferation, introducing a specific term in the model equation for cancer cells.

2. The model

We consider a fixed volume domain $\Omega \subset \mathbb{R}^3$ as our biological system, with confined chemical species in it having densities $s_i = s_i(\boldsymbol{x}, t)$, for $i = 1 \dots n$, at time $t \in (0, T]$ and position $\boldsymbol{x} \in \Omega$. Let S be the Ω bounding surface, if $\boldsymbol{s} = (s_1 \dots s_n)$, then [33]

$$\frac{d}{dt}\int_V s_i(\boldsymbol{x}, t)dx = -\int_S \boldsymbol{\varphi}_i(\boldsymbol{x}, t)\cdot d\boldsymbol{S} + \int_V f_i(\boldsymbol{s})d\boldsymbol{V} \tag{1}$$

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